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14. ABSTRACT

Epidemiological observations indicate that breast cancer risk is lower in visually impaired women compared to sighted women and that risk is inversely correlated with degree of visual impairment. A hypothesis to explain these findings is that blind people are less susceptible to suppression of melatonin by light exposure at night and therefore have higher levels of melatonin. Melatonin has oncostatic properties in vitro. In a survey of blind women, we will test the hypothesis that 1) the distribution of known reproductive risk factors for breast cancer among blind women will be consistent with lower risk when compared to the general population. In a subset of 240 women, we will test the hypotheses that 2) urinary melatonin levels are lower and estrogen levels are higher among blind women with light perception compared to women without light perception; 3) melatonin levels will be higher and estrogen levels lower among totally blind women who have non-24-hour melatonin rhythms and therefore a confirmed absence of light-induced suppression of melatonin, compared to totally blind women who have 24-hour melatonin rhythms and may be affected by light.

15. SUBJECT TERMS
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INTRODUCTION

Since 1940, breast cancer incidence rates have been steadily rising in the United States (1). There is growing evidence for possible effects of exposure to light at night (LAN) on cancer risk due to the increased use of modern electric lighting (2-8). Epidemiological observations indicate that breast cancer risk is lower in women who are visually impaired as compared to the sighted population and that the risk may be inversely correlated with degree of visual impairment (9-13). One hypothesis proposed to explain these findings is that blind people are less susceptible to suppression of melatonin by light exposure at night and therefore have higher circulating levels of melatonin. Melatonin has been shown to have oncostatic properties in vitro (14). Frequent light-induced melatonin suppression has been hypothesized as a cause of the higher breast cancer incidence observed in female shiftworkers and flight-attendants (3-6,15-17). Blindness is also associated with disorders of the circadian system (18) and changes in reproductive function (19-20) which may also contribute to breast cancer risk. The aim of this study is to investigate further the relationship between the severity of blindness and melatonin and estrogen production while simultaneously assessing how blindness and/or melatonin production are related to known risk factors for breast cancer.

BODY

The study design and approved Statement Of Work is divided into two parts; Part 1 is an epidemiological health survey of breast cancer risk, with the aim of recruiting 12,000 blind women and Part 2 is an assessment of melatonin and estrogen levels in a subset (240, or 2%) of the women.

Statement of Work progress report

No-cost extension

We recently requested and obtained a 12-month 'no-cost extension' to the grant (see 'Modification of Contract' dated 12 March 2007). As outlined in our request, we required additional time to complete data analysis due to the initial delays in obtaining HSRRB approval and maternity leave by the senior research assistant.

Part 1 – Epidemiological Survey of Cancer in the Visually Impaired

Task 1 (Months 1-4). Task 1 has been completed as described in previous reports.

Task 2 (Months 5-12). Task 2 has been completed as described in previous reports.

Task 3 (Months 12-24) – Data collection.
a,b,c,e) Tasks 3 a-c and e have been completed. We completed a second round of advertising, including advertisements or interviews in Braille Forum, Braille Monitor, radio reading services and several hundred associations and institutions for the visually impaired nationwide. As a result of these efforts, we have extended our survey population to a final total of 1400 blind female subjects. While our initial aim was to study 12000 women, our recruitment rates have been lower than anticipated and, although we have reached a high proportion of the national visually impaired population, and our study is well known within the visually impaired community, these efforts have not yielded the recruitment rate that we expected. We estimate that our advertising in Braille Forum and Braille Monitor reached approximately 40,000 visually impaired women, in addition to advertising placed in many other forums. The resultant response rate of ~3-4% is unfortunately lower than anticipated.

While modest, these data do represent the largest and most detailed survey of factors affecting breast cancer risk in visually impaired women conducted and will permit detailed analyses of the relationships between visual impairment, reproductive history and breast cancer risk factors. All the data have been entered into our database and has been cleaned and coded. Analysis is currently underway

d) Given the lower than expected recruitment rate for the main survey, we have not initiated a repeat prospective study as the numbers would be too modest for meaningful prospective analysis.

Task 3 – Data analysis (Months 25-36).
a) Data entry and coding has recently been completed for all data; b) Preliminary descriptive statistics have been compiled for all data (see report below). Formal analysis will begin shortly and is due for completion by October 2007; c) The final report and manuscripts describing major findings from the Y1 and Y2 data combined will be submitted over the next 12 months.

d-h) As described above, our recruitment rates are substantially lower than initially anticipated and precluded the completion of a third call for volunteers, as planned, and establishment of a prospective cohort.

Part 2 – Assessment of Melatonin and Estradiol Levels in the Visually Impaired

Task 1 (Months 1-4). Task 1 has been completed as described in previous reports.

Task 2 (Months 5-12). Task 2 has been completed as described in previous reports.

Task 3 (Months 13-36). Task 3 has been completed. A total of 130 visually impaired women have completed the field study. Each subject has completed a daily sleep diary and worn a wrist-borne activity monitor for 8 weeks, and have completed sequential 4-8 hourly urine collections for 48 hours on 2-3 occasions. These 130 subjects represent ~10% of the survey population and the high proportion of subjects studied will allow a detailed comparison on the physiological and epidemiological data. We had originally intended to study 2% of the survey population (240 subjects of the intended n=12,000) but the initial delay in the HSRRB response meant that we could only collect field data for two years rather than three intended.

Task 4 (Months 12-36). Task 4 is ongoing. a-d) Data entry and plotting of sleep-wake times has been completed. Urinary assays for 6-sulphatoxymelatonin have been completed for 98/130 subjects. Urinary assays for estrone-3-glucuronide have been completed in 27 subjects with the remainder scheduled for summer 2007. Preliminary analysis has been completed on a subset of subjects (see report below) and we anticipate completing all analysis by October 2007, and the submission of manuscripts and the final report by May 2008.

Research findings for the period of the report

Part 1 – Epidemiological Survey of Cancer in the Visually Impaired

Methods
The primary reporting tool for this cross-sectional study was an epidemiological survey (see Appendix A in annual report 2005). The survey consisted of 126 questions about known breast cancer risk factors ranging from reproductive risk factors (e.g. age of menarche, menopause, first childbirth, lactation) to factors such as diet, alcohol use, body habitus, exercise and family history. The survey also contained questions about visual impairment including diagnosis, current eye conditions, visual acuity, degree of light perception and age of onset of visual impairment. The survey included the Harvard National Depression Screening Scale (HANDS) and socioeconomic questions. Finally, the survey included the Pittsburgh Sleep Quality Index (PSQI) and additional sleep questions to determine the presence of a circadian sleep disorder.

The survey was provided in a variety of formats including Braille, large print, audio, via the internet, e-mail or verbally over the telephone. The web-based survey was developed by Velir studios and is compliant with US section 508 (Americans with Disabilities) guidelines for web pages. The survey was also rigorously tested by over 20 blind computer users with varying degrees of vision, computer skills and assistive technologies. The web-based survey also served as a study database

and surveys completed in other formats were entered by research staff. The survey was compliant with Health Insurance Portability and Accountability Act (HIPAA) privacy standards by separating identifiable information from survey information on two separate servers. Ethical permission for the study was granted from the Institutional Review Board at Brigham and Women's Hospital and the United States Department of Defense Human Subjects Research Review Board. Informed consent was obtained from all subjects.

Test survey entries, duplicate subject survey entries, data from subjects who completed <30% of the survey and data from male participants were removed from the analysis. Data were sorted and answers open ended survey questions were coded to correct misspellings and ensure consistency between responses. For example, all subjects reporting 'retrolental fibroplasia' as the primary eye condition were recoded to the 'retinopathy of prematurity' group. Descriptive statistics were compiled using Intercooled Stata Version 8.2 software (StataCorp LP, College Station, Texas, USA). No formal interim statistical analysis has been performed on the epidemiological survey data in order to avoid the need for adjusting the statistical probability in the final primary analyses. These formal analyses will be completed by October 2007.

Results

Visual impairment

A total of 1392 subjects completed the survey; 967 subjects reported some degree of light perception (LP), 396 reported being unable to perceive light (NPL) and 29 did not report degree of light perception. LP subjects were further classified by their reported degree of light perception from corrected vision in the better eye as; able to see the top letter on the vision chart (n=450), able to count fingers (n=200), able to see shadows and hand movement (n=157), light perception only (n=160). Of the NPL subjects, 103 reported having both eyes enucleated.

Age and BMI

The mean age of the entire cohort was 56.81 years (± 17.79) and mean age increased with respect to menopausal status, as expected (Table 1). The BMI for the entire cohort was overweight at 29.0, with the average weight for the cohort as 163.98 (± 44.18) pounds and the average height was approximately 5 ft. 4 in. (± 3.05) (Table 1).

Sleep Disorders

The mean PSQI score (range 0-21, with a score of ≥5 indicating a sleep disorder) generally increased with age and menopausal status and was elevated in all groups, with a cohort mean of 7.20 (± 4.09) (Table 1).

Table 1. Demographic data and PSQI scores for subjects sorted by menopausal status.

Menopausal Status	N	Age (n)		Weight (n)		Height (n)		BMI	LP/NPL/ Unreported	PSQI Score (n)	
Pre-menopausal	384	37.52 (380)	±10.31	164.79 (382)	±48.65	63.73 (381)	±3.03	29.2	273/106/5	6.66 (336)	±3.77
Peri-menopausal	155	51.73 (154)	±5.93	176.88 (154)	±44.05	63.13 (153)	±3.21	31.4	99/52/4	8.09 (137)	±4.42
Post-menopausal	811	66.97 (804)	±13.70	160.20 (801)	±40.50	63.43 (802)	±2.92	28.3	565/228/18	7.32 (693)	±4.12
Unreported	42	55.31 (42)	±16.67	181.80 (41)	±56.36	64.88 (40)	±4.39	31.2	32/10/0	6.38 (26)	±4.79
Entire Cohort	1392	56.81 (1380)	±17.79	163.98 (1378)	±44.18	63.52 (1376)	±3.05	29.0	969/396/27	7.20 (1192)	±4.09

Data are mean ± SD; PSQI = Pittsburgh Sleep Quality Index, score ≥ 5 indicates sleep disorder; BMI = Body Mass Index, underweight = 18.5-24.9, overweight =25.0-29.9, obese ≥ 30.

The PSQI scores do not appear to be associated with degree of light perception for subjects who reported light perception, however NPL subjects had a higher mean PSQI score than combined LP subjects (Table 2). Subjects who had both eyes removed had the highest mean PSQI score (7.69 ±4.21) as compared with those who had one or no eyes removed (Table 3).

Table 2. PSQI scores sorted by degree of visual impairment.

Level of Vision	N	PSQI Score		Age	
Eye Chart	450	6.91 (385)	±4.08	60.21 (445)	±18.81
Counting Fingers	200	6.83 (173)	±4.11	60.4 (200)	±19.68
Shadows/Hand Movement	157	7.32 (144)	±4.06	54.31 (156)	±20.27
Light Perception Only	159	6.86 (136)	±4.22	51.45 (157)	±15.55
LP	966	6.96 (838)	±4.10	57.85 (958)	±13.50
NPL	396	7.81 (334)	±4.02	54.10 (393)	±14.22
Unreported	29	7.35 (20)	±4.08	58.90 (29)	±13.50

Table 3. PSQI score scored by the number of intact eyes

Eyes Enucleated	N	PSQI Score	
None	987	7.14	±4.08
One	90	7.38	±4.11
Both	103	7.69	±4.21
Unreported	12	7.08	±4.36

Reproductive function and history

The mean age of menarche did not appear to vary with degree of light perception, though subjects reported vision loss before age 12 had a slightly earlier menarche compared to those who lost their vision after age 12. NPL subjects appeared to reach menarche at a slightly younger age than LP subjects. NPL subjects also reported a slightly later menopause compared to LP subjects (Table 4).

Table 4. Demographic data and PSQI scores for subjects sorted by menopausal status.

		Puberty			Menopause		
LP/NPL	Age of Visual Loss	N	Mean Age		N	Mean Age	
LP	Visual Loss < 12	480	12.28	±1.60	253	44.45	±9.75
	Visual Loss ≥12	458	12.74	±2.36	365	47.62	±7.77
	All	938	12.50	±2.02	618	46.33	±8.77
NPL	Visual Loss < 12	312	12.08	±1.40	208	48.69	±7.50
	Visual Loss ≥12	78	12.46	±1.88	51	45.90	±8.51
	All	390	12.16	±1.51	259	46.53	±7.70
Unreported	Visual Loss < 12	18	12.39	±1.42	14	46.50	±6.30
	Visual Loss ≥12	10	12.80	±1.75	9	53.11	±8.94
	All	28	12.53	±1.53	23	49.09	±7.96

Approximately 17% of the total cohort reported having a hysterectomy representing 28% of the post-menopausal subjects. Slightly more LP subjects reported having a hysterectomy (17%) than NPL subjects (15%).

Cancer history

Approximately 83% of the cohort did not report a diagnosis of any cancer. Of the remaining 17%, a history of breast cancer was most commonly reported (5.8%), followed by retinoblastoma (2.1%), basal or squamous skin cancer (2.1%), colorectal cancer (1%), melanoma (1%) and ovarian cancer (0.8%), with others totaling 4%. The reported lifetime incidence of breast cancer appeared to be ~50% lower in subjects without light perception (NPL; 3.5%) as compared to those women with light perception (LP; 6.8%) (Table 5).

	N	% Reporting BC
Vision Chart	20	4.44%
Counting Fingers	20	10.00%
Shadows	13	8.28%
LP Only	13	8.13%
LP Total	66	6.83%
NPL	14	3.54%
Unreported	1	3.45%
Total	81	5.82%

Table 5. Reported history of breast cancer (BC) according to visual impairment.

Part 2 – Assessment of Melatonin and Estrone Levels in the Visually Impaired

Methods

Sleep and urinary hormone data collection

A total of 130 subjects have completed a sleep, nap and (in pre and peri-menopausal women) menstrual cycle diary for eight weeks. Subjects also wore an activity monitor continuously during the eight week period. All subjects completed two or three 48h sessions of urine samples. The first set of samples was collected after subjects completed the sleep diary for two to four weeks. The second set of samples was collected four to six weeks following the first set. Our preliminary analysis indicated that in some NPL subjects, it was difficult to establish the period of the circadian rhythm of melatonin with 4-6 weeks between the urine sampling episodes if their endogenous circadian period was too slow. For example, it would take 4 weeks for someone with a circadian period of 24.86 h to complete a full beat cycle such that their melatonin rhythm may appear not to have changed between the

sampling episodes whereas in actuality, their rhythms had passed completely through a 24-hour cycle. In most cases, the sleep diary data will indicate whether a non-24-hour rhythm is present (see Figures 3-4 below), but in order to provide better accuracy, we collected a third set of urine samples between the other two that would be stored and only analyzed if there was any ambiguity in the result based on the two original sampling episodes.

The subjects were instructed to collect all urine over the course of each 48-hour episode in four hourly bins throughout the waking period and eight hourly periods throughout the sleep period. Subjects were instructed to collect urine starting after the first morning void on the first day of collection. They were instructed to weigh each sample using speaking scales at the end of each sampling window and were instructed to pipette a small sample from each window into a 7ml tube and immediately freeze each sample. Subjects were asked to record the times of each void, the sample window and the total urine volume for each sample period. Subjects were not asked to alter any lifestyle habits throughout the study.

6-sulphatoxymelatonin (aMT6s) and estrone-3-glucuronide (e3g) assays and analyses

Urinary aMT6s concentrations were measured by Stockgrand Ltd., University of Surrey (Guildford, UK) RIA using the method of Aldhous and Arendt. Urinary e-3-g concentrations were also measured by Stockgrand Ltd, using a commercially available ELISA. All samples from an individual were measured in a single assay.

The mean 24h aMT6s and e-3-g outputs were calculated for each subject for each sample period. Data were grouped by degree of light perception and by menopausal status (pre, post-meopausal). For analysis of the circadian rhythms, data were converted into micrograms per hour for each 4-8 hourly collection period in. Data for each subject and sample period were plotted and subjected to cosinor analysis (software provided by Dr. D. S. Minors, University of Manchester, Manchester, UK) to provide the acrophase (peak) time and the amplitude of the urinary rhythm. Only results that showed a significant fit to the cosine curve ($P<0.05$) were used to assess entrainment. Subjects were considered normally phased if the mean of the two acrophase times for aMT6s fell within the normal range as described in Lockley et al., 1997 (range; 1.3-7.1)(18). Subjects were considered 'abnormally phased' if the mean of the two acrophase times fell outside the normal range.

Results

6-sulphatoxymelatonin and estrone-3-glucoronide 24-h production in visually impaired women

The results are shown for the first 27 subjects studied; 14 pre-menopausal subjects (mean age $\pm$ SD = 40.1 $\pm$ 7.9 yrs) and thirteen post-menopausal subjects (55.8 $\pm$ 4.3 yrs) were studied as described above. All 27 subjects produced measurable amounts of aMT6s and e-3-g. There were no differences in the total amount/24 hours for either hormone when compared between those with (LP) and without (NPL) light perception. When categorized according to menopausal status, however, significant differences emerged. On average, post-menopausal women produced significantly more aMT6s (23.1 $\pm$ 13.4 ng/24 h) and significantly less e-3-g (29.2 $\pm$ 13.4 ng/24 h) than pre-menopausal women (14.5 $\pm$ 10.8 μg/24 h and 86.4 $\pm$ 45.5 ng/24, respectively). Correlation analysis showed a significant negative relationship between aMT6s and e-3-g levels in pre-menopausal women (R^2= 0.495, $p < 0.01$, Figure 1A), which persisted at during both the follicular and luteal phases of the menstrual cycle. A similar relationship was not observed in the post-menopausal subjects, primarily due to the low estrone levels (Figure 1B). These data provide encouraging preliminary evidence that melatonin and estrogen are reciprocally related

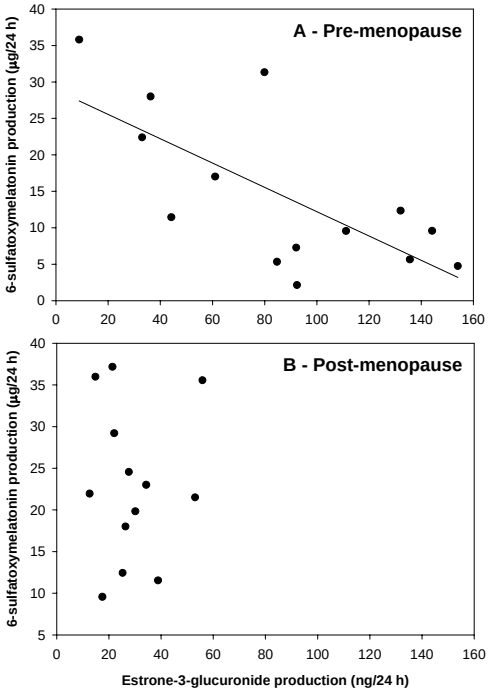

Figure 1. Urinary aMT6s and e-3-g production / 24 h in pre- and post-menopausal visually impaired women.

and that the reduction in estrogen production associated with menopause results in higher melatonin production.

6-sulphatoxymelatonin and estrone-3-glucoronide 24-h production in pre-menopausal sighted women
Preliminary observations of the e-3-g rhythms in the visually impaired subjects were ambiguous as to whether an endogenous diurnal or circadian rhythm was apparent. In order to address this question more thoroughly prior to conducting assays on all the visually impaired subjects, we analyzed urine samples from 15 healthy, sighted pre-menopausal women collected during a separate NIH-supported study under controlled laboratory conditions (28,29). The women were studied for three days under normal baseline conditions (8 h sleep and 16 h wake) before undergoing a 50-hour constant routine procedure designed to assess endogenous circadian rhythms in the absence of external time cues (30). The procedure requires the subjects to remain awake in constant dim light (<3 lux) in a semi-recumbent posture with daily nutrients spread evenly between 24 hourly snacks. The procedure is the gold-standard for assessment of endogenous circadian rhythms (30). Urine samples were collected and processed as described in the field studies.

As expected, a strong diurnal (baseline conditions) and circadian (constant routine conditions) rhythm in urinary amt6s was observed with a night-time peak (see Figure 2). In addition, a diurnal and circadian rhythm was also observed for e-3-g but with a day-time peak, approximately 180° out of phase with the night-time urinary melatonin rhythm (Figure 2). These data represent the first evidence of an endogenous circadian rhythm in estrogen and have major implications for understanding the relationship between melatonin and estrogen endocrinology, in addition to prompting a reevaluation of how estrogen levels are sampled and interpreted for epidemiological and physiological studies. For example, a morning void sample in the current study would have indicated a negative relationship between high levels of melatonin and low levels of estrogen. An afternoon urine sample would have shown the opposite negative relationship, however, with low melatonin and high estrogen levels.

Future analyses of data from these subjects will evaluate whether the relationship between melatonin and estrogen is associative or causative. We will analyze whether the suppression of melatonin by ocular light exposure directly elevates estrogen levels. If found to be the case, these data would provide evidence for a mechanism by which light exposure at night may increase breast cancer risk in female shiftworkers directly through elevated estrogen production, a known risk factor for breast cancer, in addition to any change in the oncostatic role of melatonin.

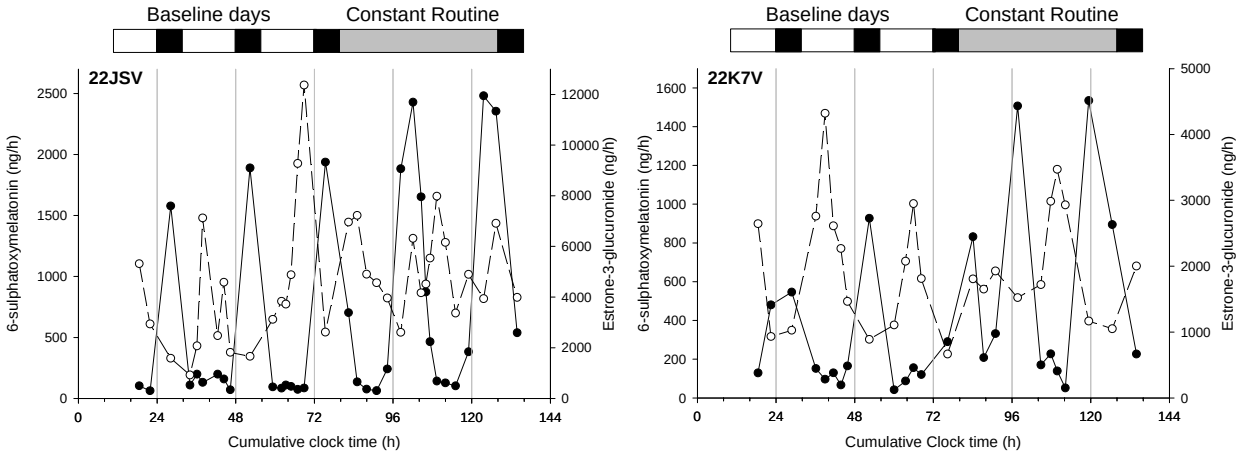

Figure 2. Representative examples of urinary aMT6s (●) and e-3-g (○) rhythms in two pre-menopausal sighted females during the luteal phase of their menstrual cycle (22JSV and 22K7V). Study conditions during the 5 study days (0-144 hours) are shown by the bars at the top of each graph with three baseline days with 16 h wake (□) and 8 h sleep (■) followed by a 50-hour constant routine (CR) (■). There is clear rhythm in aMT6s with a night-time peak under both diurnal (baseline) and circadian (CR) conditions. There is also a clear rhythm in e-3-g but with a day-time peak.

6-sulphatoxymelatonin circadian rhythmicity

When assessed by cosinor analysis, 10 subjects included in the present analysis showed a significant aMT6s rhythm. Of these subjects, three reported some degree of light perception, six reported having no light perception and one subject did not report degree of light perception. Two of the LP subjects and one of the NPL subjects were classified as normally phased (mean acrophase within normal range 1.3-7.1). Three of the NPL subjects were classified as not abnormally phased (mean acrophase outside the normal range) and the remaining subjects could not be classified by circadian phase. Figures 3-4 show representative plots of the self-reported sleep and nap diary and results of aMT6s rhythms for 2 subjects, one with normally phase rhythms (Figure 3) and one with non-entrained circadian rhythms (Figure 4). Similar analyses are ongoing for the remaining subjects for both aMT6s and e-3-g rhythms and are due for completion by October 2007. Once completed, these subjects will be categorized into those with and without circadian photoreception, with the latter based on the presence of non-24-hour rhythms and/or bilateral enucleation, before analysis of aMT6s and e-3-g production.

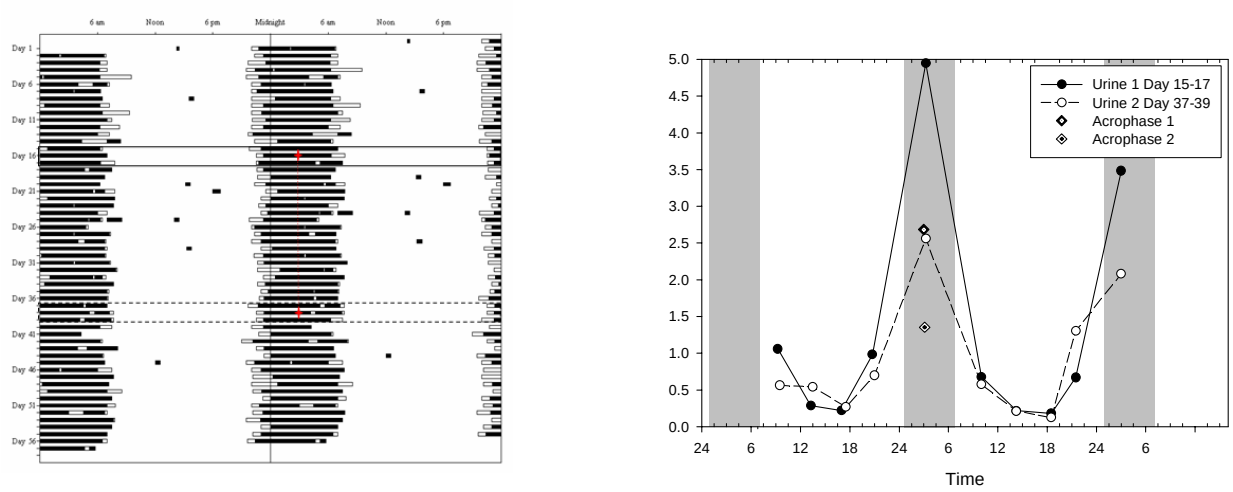

Figure 3. Representative raster plot and 48h aMT6s profile for a normally phased pre-menopausal LP subject. A) Raster plot of self reported sleep and nap times. Data are double plotted with clock hour across the top and day of study on the y axis. Black bars indicate sleep, open bars indicate times awake in bed. The solid black bracket encases the sampling days for the first set of urine samples and the dashed bracket encases the sampling days for the second set of urine samples. Red stars indicate aMT6s acrophase times taken from cosinor analysis. The line connecting the acrophase times is for visual orientation only. B) 48h aMT6s profile in micrograms per hour. Filled circles correspond to the first urine sample period, open circles correspond to the second urine sample period. Diamonds represent acrophase times as assessed by cosinor fit and shaded areas indicate the range of normal acrophase time.

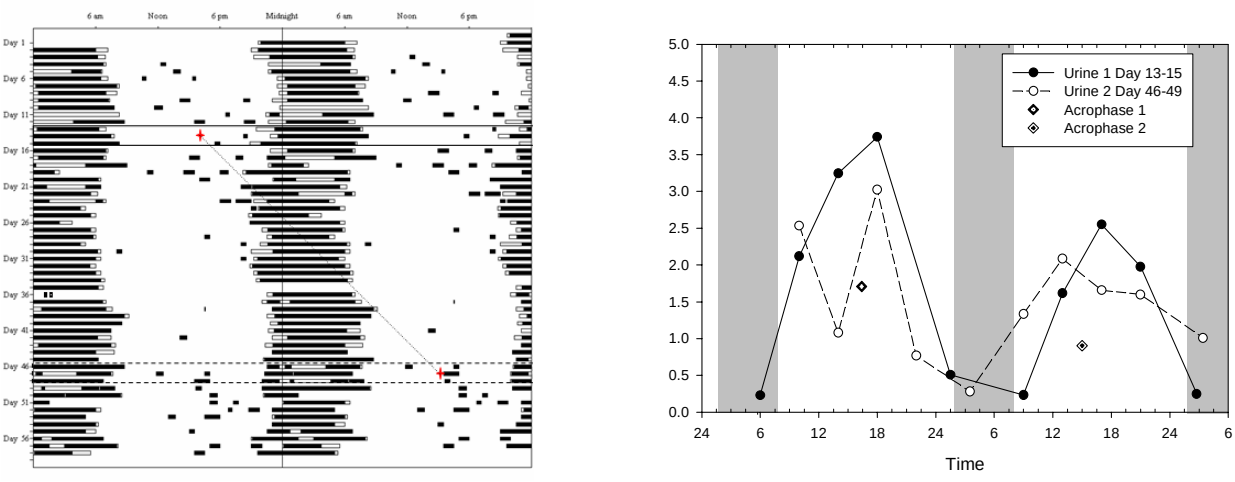

Figure 4. Representative raster plot and 48h aMT6s profile for an abnormally phased pre-menopausal NPL subject with a non-entrained circadian system (key as for Fig 3). Note that the peak aMT6s time is delayed during the second collection compared to the first and is accompanied by daytime napping. The characteristic cycling of episodes of good sleep (days 26-46) and bad sleep (days 1-25 and 47 to 58) indicative of non-24-hour sleep wake disorder is easily observed.

Problems encountered in accomplishing the Statement Of Work

We have not been able to achieve the anticipated recruitment rate to date for the epidemiological survey. We had hoped to establish a database with 12,000 participants but only 1400 have completed the study, despite reaching ~40,000 visually impaired women by conservative estimate based on several nationwide appeals. While this study still represents the largest and most comprehensive database of breast cancer risk factors in the visually impaired constructed to date, the relatively numbers preclude development of a prospective cohort as we had originally planned.

KEY RESEARCH ACCOMPLISHMENTS

- We have surveyed 1392 visually impaired women and established a database addressing a wide range of risk factors associated with breast cancer in this population
- Preliminary analysis suggests that blind women may have a lower prevalence of breast cancer than sighted women, and that prevalence is lowest in those women with no light preception
- We have studied 130 blind women under field conditions and analyzed data from 15 sighted women studied under controlled laboratory conditions to establish the relationship between the degree of blindness and melatonin and estrogen endocrinology. Two important findings have emerged to date:
    - We have found a significant reciprocal relationship between urinary melatonin and estrone output/24 hours in visually impaired pre-menopausal women. Future analyses will establish whether this relationship is associative, or whether manipulation of melatonin synthesis by light can affect estrone production.
    - Preliminary analysis suggests that there is an endogenous 24-hour rhythm in estrone-3-glucuronide under the control of the circadian pacemaker with a day-time peak, 180° out of phase with the melatonin rhythm. This finding has extremely important implications for how estrogen is sampled in epidemiological and physiological studies and may initiate a major review of current techniques and findings in this area.
- In addition, we ran two summer undergraduate training programs in circadian biology and breast cancer and an ongoing undergraduate volunteer program that combined, have been completed by more than 20 undergraduate students.

REPORTABLE OUTCOMES

Databases

As described above, we have constructed a database of 1400 visually impaired women for the assessment of risk factors associated with breast cancer including visual impairment, reproductive function and history, diet and circadian rhythm desynchrony.

Abstracts and Presentations

2004 Lockley SW. Circadian rhythms in blind women. Circadian Disruption and Breast Cancer Meeting; 2004 Jul 9-11; Chapel Hill.

2005 Evans EE, Schernhammer ES, Silver ES, Stevens RG, Lockley SW. Reproductive and hormonal risk factors for breast cancer in blind women. Dana-Farber/Harvard Cancer Center Cancer Disparities Program, New Investigators Poster Session; 2005; Apr 15; Boston,

2005 Lecture Series: Reproductive and hormonal risk factors for breast cancer in blind women Summer undergraduate program (10 x 3-h lectures), Division of Sleep Medicine, Brigham and Women's Hospital; 2005; Jun 1-Aug 16; Boston.

2005 Evans EE, Schernhammer ES, Silver ES, Stevens RG, Lockley SW. Reproductive and hormonal risk factors for breast cancer in blind women. Era of Hope Department of Defense Breast Cancer Research Program Meeting; 2005; Jun 8-11; Philadelphia

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CONCLUSIONS

In summary, while no conclusions can be drawn at this time between breast cancer risk and visual impairment, there are preliminary data suggesting that blind women do have a reduced incidence and that it is lowest in totally blind women. We have found preliminary evidence for a negative relationship between melatonin and estrogen in pre-menopausal women, and that melatonin levels are higher in post- compared to pre-menopausal women, also suggesting a reciprocal relationship between melatonin and estrogen. Furthermore, we have discovered a circadian rhythm in estrogen that is 180° out of phase with the melatonin rhythm, also consistent with a negative relationship between these two hormones. Further work will confirm whether this is an associative or causative relationship, and potentially provide a new avenue for research into the environmental risk factors for breast cancer and possibly new preventative initiatives.

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